REMARKS

Claims 42-47, 49-53, 56-57, 82-85, 90, 92, 94, 96, 98, 100 and 102-103 are pending for examination with claims 42, 44, 82, 90, 92, 94 and 96 being independent claims. Claim 82 has been amended to clarify that the C is unmethylated. Support for this amendment is found throughout the specification in the teachings that an unmethylated CpG motif confers immunostimulatory activity on an oligonucleotide. Claims 92 and 94 have been amended to add the limitation that at least one internucleotide linkage has a phosphate backbone modification. Claim 96 has been amended to add the limitation that the nucleic acid has a length of 8 to 100 nucleotides. No new matter has been added.

Rejections under 35 U.S.C. §112

Claims 42-47, 49-53, 56-57, 82-85, 90, 92, 94, 96, 98, 100 and 102-103 have been rejected under 35 U.S.C. §112 for a lack of enablement.

The Examiner has maintained the rejection of the claims of record under 35 U.S.C. §112. Pages 2-10 of the Office Action dated March 29, 2006 repeat the rejection found in the Office Action dated June 28, 2005 with the exception that the rejection based on several of the papers that were cited in support of the lack of enablement rejection has been dropped. Applicants thank the Examiner for the acknowledgment that the rejection based on unpredictability supported by such references has been withdrawn. Pages 10-14 of the Office Action address the Examiner's reasons for maintaining the rejection for lack of enablement. Each of these issues is addressed herein. The reasons for maintaining the rejection are addressed first.

Response to the Examiner's reasons for maintaining the rejection:

a. variability in the data

Initially the Examiner has pointed to variability in data found in the specification and submitted with the Declaration of Dr. Arthur Krieg in response to the prior Office Action. According to the Examiner, such variability is supportive of the unpredictability of the claimed invention, and in particular the scope of CpG oligonucleotides encompassed by the claims.

As explained in the declaration of Dr. DeSanctis, submitted with the prior response, variability in human data is expected when humans are treated with virtually any drugs. Humans are an outbred population, genetically diverse, and humans respond with great variability to drugs. This is particularly the case where the immune system is involved. Humans have an immune status that fluctuates much more than the mice used in experimental research. A human's immune status on any particular day can determine the human's response to a drug. One of ordinary skill in the art would have expected the type of variability seen in the data of the specification as well as the data presented with the Krieg declaration and would not have altered the conclusion that CpG containing oligonucleotides would have the ability to initiate *in vivo* a pattern of cytokine release which would drive the immune system toward a Th1 response.

Specifically, the Examiner has stated that "the data in both Table 4 and Example 12 shows that in each experiment there were several ODNs that had a stimulation index the same as or lower than the ODNs without a CG motif (#1982 for example)." (Office Action page 11).

The basis for the rejection with respect to Example 12 is not understood. Only one CpG oligonucleotide was tested in Example 12 and it was not #1982. The data in Example 12 (Figures 9-15) demonstrate a consistent therapeutic effect whereas the control (non-CpG oligonucleotide) does not. Figures 9 and 10 show that the CpG oligonucleotide maintained cell count at a level close to that of the saline control, whereas the allergen administered without the CpG oligonucleotide dramatically increased cell count. Figure 11 shows that the CpG oligonucleotide resulted in an eosinophil count similar to that of that of the saline control, whereas the non-CpG oligonucleotide (control oligo) resulted in an eosinophil count similar to that induced by the allergen alone. Figure 12 shows that the ability of CpG oligonucleotides to suppress eosinophil infiltration is dose dependent but still occurs even at very low levels of oligonucleotide. Figure 13 shows that the resultant inflammatory response from allergen exposure correlates with the levels of the Th2 cytokine IL-4 in the lung and that the CpG oligonucleotide maintains suppression of IL-4 expression. Figures 14 and 15 show that administration of the CpG oligonucleotide can redirect the cytokine response of the lung to production of IL-12 and IFN-γ, indicating the Th1 type of immune response. It is unclear what variability the Examiner is referring to in Example 12. She is

respectfully requested to withdraw the rejection as there is no apparent basis in Example 12 for this rejection.

The basis for the rejection with respect to Table 4 is also not understood. Table 4 includes a comparison of a single data point with a CpG oligonucleotide (SEQ ID NO 6) versus E. coli DNA, calf thymus DNA, and a non-CpG oligonucleotide. The CpG oligonucleotide and E. Coli DNA induced high levels of IL-6 while the non-CpG control oligonucleotide and calf thymus DNA did not. It is unclear what variability the Examiner is referring to in Table 4. She is respectfully requested to withdraw the rejection as there is no apparent basis in Table 4 for this rejection.

The Examiner also stated that "Declarants also indicated that one of ordinary skill in the art would have expected the type of variability seen in Table 13 and would not have altered the conclusion that CpG containing oligonucleotides would have the ability to initiate in vivo a pattern of cytokine release which would drive the immune system toward a Th1 response." (Office Action page 11). "However, upon review of the additional data (Krieg declaration), it is noted that there are several ODN without a CpG motif (#1471, 1745, 1845, 1908, 1911, 1944, 1957, 1958, 1982) that induced increases in the cytokine IL-12 when incubated with PBMC. Conversely, there were several ODN (#1758, 1826, 1835, 1842, 1894, 1962, 1965, 1967, 1968, 2005, 2006, 2014) with one or more than one CpG motifs where the IL-12 levels were the same as cells only or actually decreased the level of IL-12 production." Seven of the ODN without a CpG motif increased IL-12 in Patients 3 and 5." (Office Action page 11).

Initially Applicants point out that ODN 1958 has a CpG motif and should not be included in the list of control oligonucleotides. Additionally, none of the data demonstrated a decrease in IL-12 production.

It is requested that the rejection be withdrawn, as it appears based on a faulty premise. The examiner concluded that 12 oligonucleotides including CpG motifs did not significantly induce IL-12 expression. Applicants believe the Examiner's conclusion is based on a hindsight selection of only portions of the data. The conclusions are not supported by the totality of the data, as it would be considered by one of ordinary skill in the art. The Examiner has looked only at the data from one or two of the patients for those particular oligonucleotides, not all the patients. In order to clarify the data on the record, Applicants provide a summary of each of the oligonucleotides identified by

the Examiner (#1758, 1826, 1835, 1842, 1894, 1962, 1965, 1967, 1968, 2005, 2006, 2014) as not resulting in increased IL-12 levels:

1758: 4 of 6 patients exhibited increased IL-12 levels

1826: 4 of 5 patients exhibited increased IL-12 levels

1835: 4 of 7 patients exhibited increased IL-12 levels

1842: 6 of 7 patients exhibited increased IL-12 levels

1894: 3 of 5 patients exhibited increased IL-12 levels

1962: 5 of 8 patients exhibited increased IL-12 levels

1965: 3 of 5 patients exhibited increased IL-12 levels

1967: 3 of 5 patients exhibited increased IL-12 levels

1968: 2 of 6 patients exhibited increased IL-12 levels

2005: 2 of 5 patients exhibited increased IL-12 levels

2006: 3 of 5 patients exhibited increased IL-12 levels

2014: 3 of 5 patients exhibited increased IL-12 levels

Additionally, 14 CpG containing oligonucleotides induced IL-12 levels in every patient tested.

Of 26 oligonucleotides tested, 14 were active in 100% of the patients tested and 10 were active in 60% or more of the patients tested. Two were active in less than ½ of the patients tested. All were active. The data taken as a whole provides strong evidence that CpG containing oligonucleotides induce IL-12 production in human PBMC.

It is concluded in the Office Action that this variability in the data would appear "to indicate that the specification does not enable the full scope of the claims where any one of the myriad CpG will be sufficient to treat an asthmatic subject as presently claimed." (Office Action page 11).

Initially, Applicants wish to point out that the Examiner indicated in the Interview Summary that she agreed that any formulation of the CG motif would activate immune response parameters. The data added by the declaration is equally supportive of this view.

There is tremendous variability in the human responses to immune factors, as well as other drugs. Applicant's have made the point that inter-patient variability exists in the prior response to Office Action and the Declaration of Dr. DeSanctis. In addition, Witt et al., (Cancer Research 53,

5176-5180 (1993)) describes a Phase I study of imiquimod in cancer patients. Table 6 shows the variability in the IFN responses to imiquimod in different humans. At certain dose levels some patients respond and others do not. Gibson et al (J. Interferon and Cytokine Research 15, 537-545 (1995)) shows high variability among human responses to imiquimod. For example, in Table 1 the E+ cells are unresponsive with some donors, and assays, but not with other donors. Additionally, the medium control in experiment 2 for TNF is higher than the response to the low concentration with some donor cells. Imiquimod is an FDA approved drug, which is widely used for treating conditions ranging from genital warts to skin cancer. Thus, despite the known variability in the responses to the drug it is used in the medical profession.

Another publication (Krown et al J Interferon Research, 3, 281-290 (1983)) shows variability in human subjects in a clinical trial with a different drug. According to the Krown et. al., reference, on page 285, last paragraph, patient 2 only demonstrated an IFN response on one occasion. The other 4 patients demonstrated IFN responsiveness as shown in Table 1. Tomai et al (Antiviral Research, 28, 253-264 (1995)) demonstrate enormous variability in monkey responses to S-28463. For example, at 0.1 mg/kg some monkeys showed no response, (Table 2, female #2), while other monkeys had a good response to the same dose (male 2).

Variability in individual experiments with individual donors is common. Variability in experiments does not lead one of ordinary skill in the art to conclude that the results are unpredictable. Rather, those of skill in the art expect some degree of variability in individual data points. One of skill in the art looks to the data as a whole to develop conclusions from the data. In this case while 12 CpG oligonucleotides demonstrated some variability in inducing IL-12 production in a few donors tested, most of these oligonucleotides demonstrated strong IL-12 production in the majority of donors tested and 14 CpG oligonucleotides demonst rated IL-12 production in each donor tested.

b. McCluskie et al.

The Examiner has also maintained the rejection under 35 USC 112 on the basis that the teachings of McCluskie et al supports a lack of predictability of the invention. According to the Examiner, the claims read on DNA vaccines because there is no upper limit to the size of the nucleic acids claimed in claims 42, 56, 57, 92, 94, 98, and 96. "The immunostimulatory nucleic

acid could read on the whole bacteria, or the immunostimulatory nucleic acid could be part of a DNA vaccine." (Office Action page 12).

The claims do not read on the use of a whole bacteria or a DNA vaccine. Pending claims 42, 56, 57, and 98 and amended claims 92 and 94 include the limitation that at least one internucleotide linkage of the nucleic acid has a phosphate backbone modification. Bacterial DNA does not have phosphate backbone modifications. DNA vaccines also do not have phosphate backbone modifications. Plasmids are double-stranded circular nucleic acids (specifically DNA) molecule of restricted size (about 1000-30,000 nucleotides) that have phosphodiester internucleotide bond chemistry. Because plasmids are produced by bacteria and have a phosphodiester bond chemistry, a plasmid cannot have a phosphate backbone modification, for example, to add stability. A bacteria is incapable of producing or replicating such a modification. Thus a claim that includes a limitation that at least one internucleotide linkage of the nucleic acid has a phosphate backbone modification does not embrace DNA vaccines or bacterial DNA.

Claim 96 has been amended herewith to incorporate the limitation that the nucleic acid has a length of 8 to 100 nucleotides. The length limitation clarifies that the nucleic acid claimed does not embrace bacterial DNA, whole bacteria or a DNA vaccine.

c. Post-filing data and Declaration of Dr. DeSanctis

The Examiner has dismissed Applicants arguments regarding the data found in PCT Publication No WO2004/016805 because it is "evidence of enablement post filing." The Examiner also questions whether the protocols set forth in this published patent application are performed in "the same manner as the experimental protocols of the pending application?" (Office Action page 13).

Applicants submitted PCT Publication No WO2004/016805 to rebut the Examiner's rejection for lack of enablement, which rejection was based on post filing references. The Examiner's use of post filing date evidence to support a rejection for lack of enablement necessitated Applicants use of post-filing data to specifically rebut that rejection. If the use of such references by the Examiner was proper for that purpose, then the use of such references by Applicants for the same purpose is proper.

The Examiner has also raised several questions regarding the Declaration of Dr. DeSanctis. The Examiner has questioned which CpG oligonucleotide is used in the data described in paragraph 15 of the DeSanctis declaration. (Office Action page 13). As set forth in the declaration of Dr. DeSanctis in paragraph 15 the CpG ODN used in the data is 5'TCG TCG TTT TGA CGT TTT GTC GTT3'.

Additionally the Examiner has asked if the experiments described in the DeSanctis declaration were "experimental methods disclosed in the Krieg application? Any data set forth in a declaration for the purposes of showing enablement of the claimed invention should indicate that the experimental compositions, method and/or protocols were disclosed in the specification, if such is the case." (Office Action page 13).

Applicants have not presented the data in the declaration for purposes of enabling the claimed invention. The data is presented to rebut the rejection of record. The specification as filed provides adequate enablement for the claimed invention. The Examiner has asserted that the invention was unpredictable at the time of filing, as evidenced by teachings found in post-filing references. Applicants have asserted that one of skill in the art would have expected the invention to work as Applicants taught in the specification at the time the patent application was filed.

The Examiner has asserted that the claimed invention was "unpredictable" and supports this view with post-filing references to show that the invention would not be expected to work even after the filing of the patent application. The data presented in the DeSanctis declaration demonstrate that the claimed methods actually do work as Applicants stated they would in the patent application. In addition, the data presented was shown to be based on the patent application and using no more than ordinary skill without undue experimentation.

The methods described by Dr. DeSanctis in his declaration follow the teachings of the specification. The specification teaches that an oligonucleotide including at least one unmethylated CpG motif (throughout the specification, i.e. Summary of the Invention) may be administered to a subject (page 19 lines 27-28) to treat asthma and reduce airway inflammation (summary of the invention, 53-54, as well as Example 12, describing a reduction in inflammatory cellular infiltrate and eosinophilia). The data described in the declaration of Dr. George DeSanctis involved an unmethylated CpG oligonucleotide administered in different dosages to cynomolgus monkeys.

Both doses of CpG oligonucleotide resulted in reversal of airway hyperresponsiveness. As stated in the declaration in paragraph 17, the Protocol described therein was known in the art in 1996. The methods and data are consistent with the teachings and data described in the specification.

It is unclear if the Examiner is requiring a higher standard. If the Examiner is requesting that the exact protocol be written out in the specification, then the Examiner is requested to provide a legal basis for such a standard. The MPEP states that the description of the experiments in the declaration should be commensurate in scope with the application "i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art." (MPEP 2164.05) The data in the declaration demonstrated the use of the compounds described in the specification in the treatment of asthma, as described in the specification using a model that was art recognized at the time the patent application was filed. No more is required.

Rejections repeated from prior office action but not addressed:

As discussed above, the Examiner re-iterated most of the rejection under 35 USC 112 presented in the prior Office Action dated June 28, 2005. Other than the specific points discussed above, the Examiner has not addressed any of Applicants' arguments filed in response to the Office Action dated June 28, 2005. Thus, Applicants present arguments to address each of these rejections again. It is specifically requested that the Examiner address each of Applicants' arguments or withdraw the rejections.

The Examiner has stated that the specification does not provide enablement for the "myriad possible immunostimulatory nucleic acids encompassed by the formulas as set forth in claims." (Office Action page 2). Over pages 2-6 of the Office Action the Examiner appears to provide 2 reasons for why the claimed class of CpG nucleic acids is not enabled.

Firstly the Examiner states that the "state of the art is unpredictable with regard to asthma treatments using CpG." The Examiner has also stated that the specification as filed fails to provide particular guidance which resolves the *known unpredictability in the art* associated with effects provided in vivo." (Office Action page 5, emphasis added).

The only objective evidence presented by the Examiner that the "state of the art is unpredictable with respect to CpG treatment" is McCluskie et al which describes DNA vaccines.

As discussed above, the claimed invention does not encompass the use of DNA vaccines. The references of record do not establish a "known unpredictability in the art".

The Examiner has the initial burden of establishing the reasons for lack of enablement. The Examiner must present evidence or explain why the accuracy of Applicants' assertions are doubtful. See MPEP section 2164.04:

> "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 USC 112 first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370."

In the instant case there is absolutely no evidence of record to establish this "known unpredictability." As discussed above, the teachings of McCluskie are not relevant to the claimed invention. The Examiner has not met her burden in establishing the rejection for lack of enablement. Mere conclusions as to "the known unpredictability in the art" is not sufficient.

The second reason advanced by the Examiner for a lack of enablement of the use of a class of CpG oligonucleotides set forth in the claims is that "one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of the successful treatment of asthma."

Applicants have presented a significant amount of data in the specification and asserted on the record that such data correlates with the scope of the claimed invention. Applicants have

included many examples in the specification including induction of cytokines such as IL-6, IL-12 and IFN-gamma. The data in the application, includes that represented in Tables 1-3, which establishes that the unmethylated CpG is responsible for the immune stimulation. More than 40 oligonucleotides were tested. The data represented in Table 5 demonstrates that the immune stimulation has the characteristic pattern of a Th1 response. Eleven different oligonucleotides induced a Th1 cytokine profile, demonstrating the consistent stimulatory effect of CpG containing oligonucleotides. The combination of these changes in immune parameters was adequate to demonstrate to one of skill in the art at the time of the filing of the priority patent application that CpG oligonucleotides would be useful in the treatment of asthma. Applicants assert that a correlation between CpG and their use in the treatment of asthma is disclosed and enabled.

MPEP section 2164.02 teaches that

> "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
>
> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)"

Applicants have presented data and asserted that it correlates with the scope of the claimed invention. The Examiner has not presented any objective evidence to demonstrate why it does not correlate.

Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered, with a Th1 response being favored. This class of oligonucleotides is described throughout the specification and their ability to produce a Th1 favored immune response is not only described (e.g., see page 8, lines 22-23 and 25-27, page 9, lines 8-9 and page

53, line 26 – page 54, line 5) but data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. Furthermore, Dr. George DeSanctis, has stated in his declaration that one of ordinary skill in the art would have expected that virtually every CpG containing oligonucleotide would have the ability to initiate *in vivo* a pattern of cytokine release which would drive the immune system toward a Th1 response. The Examiner agreed with this point in the Interview and included this affirmative statement in the Interview Summary Record.

As discussed in Applicants prior response to Office Action, a leading theory of asthma in 1996 was entirely consistent with the teachings of the present specification. The incidence and severity of asthma was steadily increasing in the developed but not in the developing countries. This increase in the developed countries was believed to be due in part to the steady decline of infectious diseases. This "Hygiene Hypothesis" of asthma is discussed in the declaration of Dr. George DeSanctis. According to Dr. DeSanctis, the rationale behind the "Hygiene Hypothesis" is that exposure to infectious organisms or exposure to antigens derived from these pathogenic organisms induce a T-helper 1 or Th1 response early in life shifting the immune response of individuals with an allergic predisposition away from a Th2 response towards a Th1 response (IL-12, INF-γ), thereby conferring protection from developing asthma. It would have been believed that the synthetic CpG containing oligonucleotides described in the Krieg application can invoke Th1 responses mimicking what occurs in nature, via infectious agents, to confer protection against asthma.

The specification includes *in vitro* data on mouse and human cells, as well as *in vivo* data. Tables 1-3 demonstrate that many different CpG oligonucleotides are capable of activating murine B cells and inducing cytokine expression in murine cells *in vitro*. Table 5 depicts an experiment in which multiple CpG containing oligonucleotides were tested for their ability to induce cytokine expression in human cells. The experiment of Table 5 demonstrated that multiple CpG oligonucleotides were capable of inducing cytokine expression and notably an IL-12 response. As concluded in the declaration of Dr DeSanctis, the data obtained in the *in vivo* experiments such as those shown in Table 4 and Example 12 was consistent with the data obtained in the *in vitro*

experiments, confirming that the pattern of cytokine release and Th1 effects could be exploited *in vivo*.

Additionally, the data need not support that every CpG oligonucleotide work equivalently or even work at all. In Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576-77, 1984 (upholding district court decision that patent on emulsion formulations was valid even though it was, in the words of the defendant, a mere "list of candidate ingredients"), it was stated: "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude...possible inoperative substances,' In re Dinh-Nguyen, 492 F.2d 856, 858-59 (C.C.P.A. 1974)." That every CpG oligonucleotide would not work equivalently or that it is possible that some rare oligonucleotides might not work at all is not a sufficient basis for rejecting the claims.

The Examiner has also indicated that a method for treating asthma using a CpG containing oligonucleotide with an allergen is enabled but that use without an allergen is not enabled. Applicants respectfully disagree.

The above-identified patent application is based on the discovery that a class of molecules that include a CpG motif promote a very specific and effective immune response. The asthmatic immune response includes activation of the innate immune system (not antigen specific) and can also, but not necessarily, involve the adaptive immune response (antigen specific). As described in the specification, CpG oligonucleotides were shown to promote NK cell activation as well as to alter profiles of cytokines, independent of antigen administration. The specification describes the use of CpG alone for therapeutic purposes based on this discovery.

The methods for treating asthma are described throughout the application in terms of the administration of CpG as a therapeutic. It is taught that an immune profile which is consistent with the promotion of a Th1 favored response is important in asthma. The experimental work examining shifts in cytokine induction were achieved using CpG alone without an allergen. For instance and as discussed in the declaration of Dr. DeSanctis, CpG oligonucleotides were used alone without antigen/allergen to produce Th1 biased cytokine induction in Table 5. No antigen was administered.

The immune system in an asthmatic person has cytokine activity that is imbalanced toward a Th2 response. One of ordinary skill in the art would have expected that CpG oligonucleotides would help restore a proper balance. CpG oligonucleotides alone would have been expected to act on the immune system to bias the cytokine profile away from a Th2 response.

The Examiner has not addressed any of Applicants arguments that the specification adequately enables a method of treating asthma using a CpG oligonucleotide whether or not it is administered with an allergen. It is respectfully requested that the Examiner provide reasoning to maintain the rejection or withdraw it.

The Examiner has also maintained the rejection in view of the lack of safety of CpG oligonucleotides or side effects associated with CpG oligonucleotide administration. In particular, the Examiner has maintained the rejection in view of Van Uden et al (Office Action page 8) for the concept that each ISS has a minimum length limitation and that potential side effects associated with treatment must be considered. With respect to the section of the paper that refers to the length of ODN, the authors do not conclude that there is a specific rule for the length of the ODN. The authors hypothesize that different lengths and flanking sequences have an impact on the activity of the ODN. The patent application as filed confirms that certain motifs and lengths are preferred. However, it is believed that any unmethylated CpG containing oligonucleotide within the scope of the claims would have the ability to initiate in vivo a pattern of cytokine release which would drive the immune system toward a Th1 response when administered in an appropriate dosage.

The examiner quotes some language from page 907 column 2 and page 908 column 1 related to the issue of side effects associated with CpG oligonucleotide administration. Each of these statements, however, is taken out of context. After the quoted section the authors point out that such side effects have <u>not</u> been observed. For example, the Examiner has pointed to the statement on page 907 that "There is always the possibility of unwanted effects of the powerful immune stimulation that ISS delivers" and compared the effects of CpG with LPS (Office Action page 8). In contrast to the implications from the language quoted in the office action, immediately following that paragraph the authors conclude

> "Although these reports demonstrate the possibility of shock in extreme cases of sensitization or concurrent LPS exposure, there has never been a reported case of

> ISS alone causing shock in any kind of healthy animal at any dose." (Page 908 column 1 lines 2-6) and
> "We and others have never observed gross inflammation in response to ISS in ODN or plasmid form in any experimental animals or humans." (page 908 first column first full paragraph)

The Examiner has also stated that Van Uden et al teaches that "ISS could cause excessive local inflammation as seen with other powerful Th1 adjuvants, such as CFA." In contrast to this statement the authors point out an experiment in which bacterial DNA complexed with CFA is injected into mice. It is concluded that

> "When the mixture is given to preautoimmune NZB/NZW F1 mice, they develop antibodies that cross-react with mammalian DNA, but surprisingly they are actually protected from their spontaneous autoimmune disease. There still are no examples of ISS directly causing any type of autoimmune disease in animal models." (page 908 paragraph bridging columns 1 and 2).

In addition to the discussion of safety issues raised with respect to the cited references, Applicants pointed out that Several Phase I and II studies have been performed in humans to date and submitted a reference describing one such trial which concluded that administration of CpG oligonucleotides had been well tolerated. Applicants discussion of the reference was dismissed by the Examiner because "the pending claims are directed to treatments for asthma and allergies, not cancer." (Office Action page 8). However, Applicants wish to reiterate that the results of this clinical trial were submitted to demonstrate that CpG oligonucleotides have been safely administered to humans, and not to demonstrate efficacy of the compounds. Concerns related to the safety of these compounds were raised in the office action. This clinical trial demonstrates that CpG oligonucleotides have been administered to humans and were well tolerated. Rather than address the point that Applicant has made regarding the safety, the Examiner has simply maintained the rejection. This is improper. The Examiner should provide reasons why Applicants arguments regarding safety have been dismissed. The Examiner is respectfully requested to address Applicants arguments or withdraw the rejection.

In view of the teaching of the instant application and the state of the art at the time of filing, Applicants submit that the claimed invention can be practiced without undue experimentation. The declaration of Dr. DeSanctis proves this is the case. Applicants have provided CpG oligonucleotide sequences that stimulate an immune response (and demonstrated a number of immune parameters *in vivo* and *in vitro*) and has provided guidance to one of ordinary skill in the art to use the CpG oligonucleotides to treat asthma. Therefore, the amount of experimentation required to practice the invention is not undue. One of ordinary skill in the art, based on the teachings in the patent application, would have reasonably expected the claimed invention to work over the full scope of the claims.

Rejection under 35 U.S.C. §103

Claims 42, 43, 45-47, 49, 50, 51, 53 and 92 have been rejected under 35 U.S.C. §103 as being obvious over USP 5726160 (McMichael) taken with Pisetsky (J. Immunology, 1996, pp. 421-413, *incorrectly listed in office action as published in 1995*).

According to the Examiner, McMichael teaches that "a composition comprising prokaryotic DNA and a pharmaceutically acceptable carrier can be used to treat subject suffering from pulmonary disease and specifically an asthmatic subject (col.1; col. 4, example IX)" and that "it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the bacterial CpG oligonucleotides as taught in Pisetsky, since the art teaches that the bacterial DNA has immunological properties, for administration to an asthmatic subject as taught in McMichael to treat pulmonary disease." (Office Action pages 15-16).

The combination of McMichael and Pisetsky does not produce the claimed invention. Neither McMichael nor Pisetsky teach a method for treating asthma. Although the Examiner has asserted that McMichael teaches a method for treating a "subject suffering from pulmonary disease and specifically an asthmatic subject", McMichael does not specifically teach treating an asthmatic subject. McMichael teaches that DNA can be used to treat a pulmonary disorder, "including cystic fibrosis, emphysema, chronic bronchitis, sinusitis, and the common cold." (column 1 lines 11-14). The Examiner has pointed to Example IX for support. Applicants disagree that Example IX demonstrates treatment of an asthmatic subject. Example IX involves the treatment of a 58 year old

woman having persistent adult rhinitis and sinusitis. It is noted in the Example that the woman had a childhood history of asthma. However, there is no indication that the woman currently had asthma and the Example specifically teaches that she had a different disorder, persistent adult rhinitis and sinusitis. There is no suggestion in McMichael that the therapies described therein would find utility in the therapeutic treatment of asthma. Additionally, there is no teaching in Pisetsky that DNA could be useful for the treatment of asthma. Thus, the claimed invention was not obvious at the time of the invention in view of McMichael and Pisetsky.

Additionally, one of skill in the art would not have combined the teachings of Pisetsky and McMichael as suggested by the Examiner. There are at least two scientific distinctions between the teachings of Pisetsky and McMichael that would prevent the combination by one of ordinary skill in the art. Initially, McMichael teaches that DNA may be used to treat pulmonary disease. Although McMichael indicates in column 1 that the DNA may be prokaryotic or eukaryotic, all ten Examples involve the use of eukaryotic DNA (calf thymus DNA) and according to column 2 lines 28-29 are the "preferred embodiments of the invention." In contrast, Pisetsky teaches, as pointed out by the Examiner, that there is "compelling evidence that bacterial DNA, in contrast to mammalian DNA, can induce a variety of responses in both normal humans as well as animals." According to Pisetsky mammalian, or eukaryotic DNA, does not stimulate the immune system but bacterial DNA, or prokaryotic DNA, does stimulate an immune response. Thus, Pisetsky teaches that only bacterial DNA can be used to stimulate an immune response and McMichael teaches that any DNA works but that mammalian DNA is preferred for reducing mucus viscosity. One of skill in the art would find these teachings to indicate different mechanisms of action and would not combine the references.

Secondly, Pisetsky teaches that bacterial DNA induces an immune response such that B and T cells are activated, macrophage are stimulated, antibody production is induced and cytokine production is induced (Page 422, left column, 1st full paragraph). There is no suggestion in Pisetsky that bacterial DNA or CpG oligonucleotides produce a Th1 biased response, reduce eosinophil accumulation, decrease IgE production or any other physiological parameters that would be associated with the successful treatment of a respiratory disease such as asthma. The only therapeutic uses for bacterial DNA or CpG oligonucleotides suggested or implied by Pisetsky are

cancer, viral and bacterial disease. Reading Pisetsky one of skill in the art would not expect that DNA which stimulates an immune response would be useful for treating pulmonary disease associated with increased mucus viscosity. McMichael, on the other hand, describes the use of DNA to decrease the viscosity of mucus secretions for the treatment of pulmonary disorders. One of skill in the art would not be motivated to substitute an immune stimulating DNA, as described in Pisetsky for the mucus viscosity decreasing mammalian DNA of McMichael to treat the pulmonary disorders of McMichael, particularly when the two described mechanisms are so different. Any suggestion that one of skill in the art would substitute the Pisestky DNA for the McMichael DNA in the McMichael method would be based on hindsight.

Applicants reiterate on the record that pending claims 44, 52, 56-57, 82-85, 90, 94, 96, 98, 100 and 102-103 have not been rejected in view of the prior art.

CONCLUSION

If the Examiner believes, after this Response, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below. If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825. No new matter has been added.

Dated: July 31, 2006

Respectfully submitted,

By _____

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